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April 26, 2000

Dockets Management Branch (HFA-305) Food and Drug Administration 5600 Fishers Lane Room 4-62 Rockville, MD 20857

CITIZEN PETITION

francisco (m. 18) Sagar

The undersigned submits this Petition, pursuant to Section 505(j)(2)(c) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 C.F.R. Sections 314.93(b) and 10.30 of the Food and Drug Administration's regulations, to request the Commissioner of Food and Drugs to make a determination that a certain opioid analgesic elixir drug product is suitable for filing under an abbreviated new drug application (ANDA).

A. Action Requested

Petitioner requests that the Commissioner of Food and Drugs make a determination that an abbreviated new drug application (ANDA) is suitable for elixir containing 10 mg hydrocodone bitartrate/650 mg acetaminophen per 30 ml.

B. Statement of Grounds

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Waxman-Hatch Act") extends eligibility for the submission of ANDA's to certain drug products identical to those approved via new drug applications, as identified in the List of Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") published by the Food and Drug Administration. Where the proposed drug product differs from the "listed drug" in one or more respects, a person may petition the Agency, under section 505(j)(2)(c) of the Act, for a determination that the proposed drug is suitable to be submitted as an ANDA.

The listed drug product that forms the basis for this petition Watson, 10 mg/650 mg (ANDA 40-094). See Orange Book, page 3-5, at Exhibit A. To the best of petitioner's knowledge, applicable U.S. patents with respect to the drug substances, hydrocodone bitartrate and acetaminophen, have expired.

OOP-1243

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The proposed drug product differs from the listed drug products only in regard to dosage form (elixir instead of tablet). Otherwise, the proposed drug product is identical with respect to active ingredients, strength, route of administration, and conditions of use.

The availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen would provide a valuable dosage alternative, particularly for those patients who have trouble swallowing tablets, the geriatric population and other situations where a liquid dosage would be preferred.

The proposed product's dosage form is the same as several other types of approved opioid analgesic drugs which are available in liquid form. For instance, Dilaudid (hydromorphone hydrochloride), NDA 19891 (*Orange Book* at 3-182); and Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), ANDA 81051 (*Orange Book* at 3-4) attached as Exhibit B.

In view of the availability of other approved opioid analgesics as elixirs and an appropriate patient base for such a form (e.g., geriatric patients), the healthcare community would benefit from the availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL. The proposed product contains the same active ingredients, at the same strength and route of administration, and would be labeled with the same conditions of use as the listed 10mg/650 mg tablets [See Exhibits C (Side-By-Side comparison of Watson insert and proposed insert) and D (Side-By-Side comparison of Watson labeling and proposed labeling)] and packaged in an appropriate container-closure system (See Exhibit E).

Based on the foregoing, Petitioner believes that an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL warrants a finding of ANDA suitability and that the commissioner should grant permission for the filing of an ANDA for a hydrocodone bitartrate and acetaminophen elixir in the strength of 10mg/650 mg per 30 mL.

C. Environmental Impact

A categorical exclusion is claimed as the granting of this Petition will result in an ANDA for a drug product that is consistent with the parameters for exclusion established in 21 C.F.R. 25.24(c)(1).

D. Economic Impact

Information under this section will be submitted if requested by the Commissioner following review of this Petition.



The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views upon which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

PHARMACEUTICAL ASSOCIATES, INC.

By: Kaye B. m. Donald

Kaye B. McDonald 201 Delaware Street Greenville, SC 29605 (864) 277-7282 Ext. 230

Enclosures:

- A. Orange Book, page 3-5.
- B. Orange Book, pages 3-4 and 3-182.
- C. Side-By-Side comparison of Watson package insert (December 1997) and proposed insert.
- D. Side-By-Side comparison of Watson and labeling and proposed labeling for hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL elixir.
- E. Description of container and closure system for hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL elixir.



Exhibit A



ACETAMINOPHEN; HYDROCODONE	BITARTRATE		ACETAMINOPHEN; HYDROCODONE BITARTRATE	
TABLET; ORAL HYDROCODONE BITARTRATE AA VINTAGE PHARMS	AND ACETAMINOPHEN 650MG; 10MG	N40143 001	TABLET; ORAL VICODIN ES AA + KNOLL PHARM 750MG; 7.5MG	N89736 001 DEC 09, 1988
<u>AA</u>	750MG; 7.5MG	FEB 22, 1996 N40157 001 APR 12, 1996 N40123 003	VICODIN HP KNOLL PHARM 660MG; 10MG	N40117 001 SEP 23, 1996
AA WATSON LABS	500MG; 2.5MG 500MG; 2.5MG	MAR 04, 1996 N81079 001 AUG 30, 1991	ACETAMINOPHEN; OXYCODONE	
<u>AA</u>	500MG; 5MG 500MG; 5MG	N40122 001 MAR 04, 1996 N89883 001	CAPSULE; ORAL OXYCODONE AND ACETAMINOPHEN HALSEY 500MG; 5MG	N40219 001
<u>AA</u>	500MG; 7.5MG	DEC 01, 1988 N40123 004 MAR 04, 1996 N81080 001	III III III III III III III III III II	JAN 22, 1998
<u>AA</u> <u>AA</u>	500MG; 7.5MG 500MG; 10MG	AUG 30, 1991 N40148 002 FEB 14, 1997	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE CAPSULE; ORAL OXYCODONE AND ACETAMINOPHEN	
<u>AA</u> AA	650MG; 7.5MG 650MG; 7.5MG	N40094 001 SEP 29, 1995 N40123 001 MAR 04, 1996	AA MALLINCKRODT 500MG; 5MG	N40199 001 DEC 30, 1998 N40257 001
<u>AA</u>	650MG; 10MG / 650MG; 10MG	N40094 002 SEP 29, 1995 N40123 002	AA VINTAGE PHARMS 500MG; 5MG	AUG 04, 1998 N40106 001 JUL 30, 1996 N40234 001
<u>w</u>	750MG; 7.5MG	MAR 04, 1996 N40122 002 MAR 04, 1996	ROXILOX FOUNCESMC	OCT 30, 1997 N40061 001
AA ZENITH GOLDLINE	750MG; 7.5MG 500MG; 5MG	N81083 001 AUG 30, 1991 N89696 001 APR 21, 1988	AA ROXANE 500MG; SMG AA + JOHNSON RW 500MG; 5MG	JUL 03, 1995 N88790 001 DEC 12, 1984
LORTAB MALLINCKRODT	500MG; 5MG	N87722 001 JUL 09, 1982	SOLUTION; ORAL	DEC 12, 1904
AA + UCB	500MG; 10MG 325MG; 5MG	N40100 001 JAN 26, 1996 N40099 001 JUN 25, 1997	ROXICET ROXANE ROXANE 325MG/5ML;5MG/5M	L N89351 001 DEC 03, 1986
NORCO + WATSON LABS	325MG;10MG /	N40148 001 FEB 14, 1997	TABLET; ORAL OXYCET AA MALLINCKRODT 325MG; 5MG	N87463 001 DEC 07, 1983
AA + KNOLL PHARM	500MG; 5MG	N88058 001 JAN 07, 1983	OXYCODONE AND ACETAMINOPHEN AN DURAMED 325MG; 5MG	N40272 001 JUN 30, 1998

Exhibit B

PRESCRIPTION DRUG PRODUCT LIST

					N CT	ETAMINOPHEN; HYDROCODONE	BITARTRATE	
		_			ACE	G [Ald I		er de la companya de
	ACET	AMINOPHEN; HYDROCODONE	BITARIKAL		n	TABLET; ORAL		
	ACLI				3	HYDROCODONE BITARTRATE	AND ACETAMINOPHEN	
	₽T.	IXIR; ORAL	- COMPACTNODUEN			EON	750MG; 7.5MG	N40149 002
	בגבו	IXIR; ORAL HYDROCODONE BITARTRATE	500MG/15ML; 7.5MG/15ML	✓ N81051 001	AA	BOH	· · · · · · · · · · · · · · · · · · ·	JAN 27, 1997
	33 L	MIKART	500MG/15ML; 7.5MG/	AUG 28, 1992		HALSEY	500MG; 5MG	N40236 001
	AA T	Milana	14 53 5 - 5300 / 1 5MT	N81226 001	AA	UVRORI	<u></u>	SEP 25, 1997
			500MG/15ML;5MG/15ML	OCT 27, 1992			650MG; 7.5MG	N40240 002
			53.0 /1 EMT.	N89557 001	AA		030HB, 7:0HB	NOV 26, 1997
			500MG/15ML; 5MG/15ML	APR 29, 1992			CEOMC - 1 DMC	N40240 001
	+	•		N40182 001	AA		650MG; 10MG	NOV 26, 1997
		mad	500MG/15ML; 7.5MG/15ML	MAR 13, 1998			750MG-7 5MC	N40236 002
	AA	PHARM ASSOC			AA		750MG; 7.5MG	SEP 25, 1997
							EARLY ENC	N40084 002
					AA	MALLINCKRODT	500MG; 5MG	JUN 01, 1995
1	TA	ABLET; ORAL		N89160 001			50010 7 FM0	N40201 001
		ANEXSIA	500MG; 5MG	APR 23, 1987	AA		500MG; 7.5MG	FEB 27, 1998
il late s De	AA	MALLINCKRODT		ALK ==/			500x0-10x0	N40201 002
i,		0.4CCD		N40084 003	AA		500MG; 10MG	FEB 27, 1998
gr i		ANEXSIA 10/660	660MG; 10MG	JUL 29, 1996			TEALS T ENG	N40084 001
2-1	AA -	+ MALLINCKRODT		00H 227	AA		750MG; 7.5MG	JUN 01, 1995
	.1.			N89725 001			500-10 D 5160	N89698 001
		ANEXSIA 7.5/650	650MG; 7.5MG	SEP 30, 1987	AA	+ MIKART	500MG; 2.5MG	
Elia 1	AA	MALLINCKRODT		36F 307			50000 F150	AUG 25, 1989 N89271 001
	-			N87757 001	AA		500MG; 5MG	JUL 16, 1986
		CO-GESIC	500MG; 5MG	MAY 03, 1982				
	<u>AA</u>	SCHWARZ PHARMA	34043	MAI OS, 11	AA		500MG; 5MG	N89697 001
	J			N87677 001				JAN 28, 1992
		HY-PHEN	500MG; 5MG	MAY 03, 1982	AA	+	500MG; 7.5MG	N89699 001
91.7	<u> AA</u>	ASCHER		MAI 05, 1552				AUG 25, 1989
		HYDROCODONE BITARTRATE	AND ACETAMINOPHEN	N40281 001	AA	+	650MG; 7.5MG	N89689 001
		HYDROCODONE BITARIRATE	500MG; 5MG	SEP 30, 1998				JUN 29, 1988
	AA	ENDO PHARMS	3001307	N40280 001	AA	+	650MG; 10MG	N81223 001
	3.00		500MG; 7.5MG	SEP 30, 1998 \				MAY 29, 1992
	AA		300007.13	N40280 002	AA	PEACHTREE	500MG; 10MG	N40210 001
			650MG; 7.5MG	SEP 30, 1998	====		.i	AUG 13, 1997
	AA.	Ø?\A:\ •	U. U. S. S. F. C.	N40280 003	AA	UCB	650MG; 7.5MG	N40134 001
	<u>ः === %</u>		650MG; 10MG	SEP 30, 1998				NOV 21, 1996
	AA		63080, 1012	N40281 002	AA	VINTAGE PHARMS	500MG; 2.5MG	N40144 002
	- 222	The state of the s	750MG; 7.5MG	SEP 30, 1998			3	APR 25, 1997
	AA	<u> </u>	750MG, 7:313	N40288 001	AA		500MG; 5MG	N89831 001
	- 202	ર્વે કુ ^{ર્} લ ક	400MG; 5MG	N40288 001 NOV 27, 1998				SEP 07, 1988
	1. A. W.		400MG, 5110	NOV 27, 1990	AA		500MG; 5MG	N89971 001
	, A.	Alfred Control of the	400MG;7.5MG	N40288 002	222		·	DEC 02, 1988
	1.75		40000, 7.5	NOV 27, 1998	Aλ		500MG; 7.5MG	N40144 001
			ADDMC - 1 OMG	N40288 003	222			FEB 22, 1996
	Α.	and the second second	400MG;10MG	NOV 27, 1998	AA		650MG; 7.5MG	N40155 001
		40 Res	SOME SMG	N40149 001	20			APR 14, 1997
	AA	EON	500MG; 5MG	JAN 27, 1997				
	4344							



<u>H</u>	YDROCORTISONE SODIUM SUCC	CINATE		u	VDDOMODDHONE HUDDOON		
	INJECTABLE; INJECTION	-		11	YDROMORPHONE HYDROCHLOF	RIDE	
	SOLU-CORTEF				INJECTABLE; INJECTION		
AP	+ PHARMACIA AND UPJOHN	EQ 500MG BASE/VIAL	N09866 003	AР	+ KNOLL PHARM	7 0× cm /c	
AP	+	EQ 1GM BASE/VIAL	N09866 004		RNOLL PHARM	10MG/MI.	N19034 001
					+	250MG/VIAL	JAN 11, 1984 N19034 002
H	IDROCORTISONE VALERATE				HYDROMORPHONE HCL		AUG 04, 1994
	CREAM; TOPICAL			AP	ABBOTT	10MG/ML	
	HYDROCORTISONE VALERAT	re.				2010/1111	N74598 001 JUN 19, 1997
AB	COPLEY PHARM	~=	N74489 001	AP	STERIS	10MG/ML	N74317 001
AB	TARO	0.00	AUG 12, 1998				AUG 23, 1995
20	IARO	0.2%	N75042 001 AUG 25, 1998		SOLUTION; ORAL		
	WESTCORT		A0G 25, 1998	AA	+ KNOLL PHARM	5.40.45° -	
AB	+ WESTWOOD SQUIBB	0.2%	N17950 001	****	, MOLL PHARM	5MG/5ML	N19891 001
	OINTMENT; TOPICAL				HYDROMORPHONE HCL		DEC 07, 1992
	HYDROCORTISONE VALERAT	E		AA	ROXANE	5MG/5ML	N74653 001
AB	TARO	0.2%	N75043 001				JUL 29, 1998
	WESTCORT		AUG 25, 1998		TABLET; ORAL	•	
AB	+ WESTWOOD SQUIBB	0.2%	N18726 001	ΑВ	+ KNOLL PHARM		
			AUG 08, 1983	7112	I MOLL PHARM	8MG	N19892 001
					HYDROMORPHONE HCL		DEC 07, 1992
HY	DROFLUMETHIAZIDE			AB	ROXANE	8MG	N74597 001
٠.	TARTEM ORAT						JUL 29, 1998
à.	TABLET; ORAL DIUCARDIN						
AB	WYETH AYERST	50MG	N83383 001	HY	DROXOCOBALAMIN		
AB	HYDROFLOMETHIAZIDE PAR PHARM	Fara			INJECTABLE; INJECTION		
==	EAR ENARM	50MG	N88850 001 MAY 31, 1985		HYDROXOCOBALAMIN		
	SALURON		MMI 31, 1983	•	+ STERIS	1MG/ML	N85998 001
AB	+ ROBERTS LABS	50MG	N11949-001				
4			•	HYI	DROXYAMPHETAMINE HYDROB	ROMIDE	
HY	DROFLUMETHIAZIDE; RESERPI	NE		9	SOLUTION/DROPS; OPHTHAL	MTO	
	PARTED. ODAT	_			PAREDRINE	utc .	
	TABLET; ORAL RESERPINE AND HYDROFLUM	/ETHIAZIOF			+ PHARMICS	18	N00004 004
BP.		50MG; 0.125MG	N88907 001				
	SALUTENSIN		SEP 20, 1985				
BP		50MG; 0.125MG	3113350 003				
. –	SALUTENSIN-DEMI		N12359 003			•	
		25MG; 0.125MG 🎉	N12359 004		,		
	š.		*				

Exhibit C

Listed Drug

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate and acetaminophen in the following strengths per 30 mL:

Hydrocodone Bitartrate, USP Acetaminophen, USP

10 mg 650 mg

In addition, the elixir contains the following inactive Alcohol, 7%, Methylparaben, ingredients: Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, and Mixed Fruit Fiavor.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α -eccxy-3methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, nonsalicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

The behavior of the individual Pharmacokinetics: components is described below.

Hydrocodone Bitartrate (Warning: May be habit forming) and Acetaminophen Taclets, USP

DESCRIPTION

Approache Channels and Sestim-Moham is supplied in tablet form for oral administration

Hydrocoche Channels and Sestim-Moham is supplied in tablet form for oral administration

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Pharmocoxinetics: The censular of the includual components is described below.

Brand Name Generic Name

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ANDA Product

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

The administration of Acute abdominal Conditions: opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Listed Drug

Hinterpospone: Following a 10 mg oral dosa of hydrocodone administered to five adult ma-superers, the mean peak concentration was 236 s 5.2 ng/mt. Maximum serum levels wer admined at 1.3 ± 0.3 nours and the fluid-fille was determined to be 3.3 ± 0.3 hours. Hydrocodor exhibits a complex pattern of metabolism including O-demethylation. N-demethylation and 6-xet reduction to the corresponding 6-d- and 6-d-hydroxymetabolities. See OVERDOSAGE for toxicity information.

See OVERDOSAGE for toxicity information

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distributed introughout most body itissues. The plasma hair-life is 1.25 to 3 hours, but may b
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by liver metatonism (conjugation) and subsequent renal exception of metabolities. Approximate
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CONTRAINDICATIONS

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WARNINGS

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Head Injury and Increased Intracranial Pressure: The resouratory depressant effects of narcot Head injury and increases intractantal resource, the resource year and increases increases in the area of their assessment to elevate deterorations, flue of sessions of a pre-existing increases in intractan pressure, flumerimer, hardough produce adverse reactions which may obscure the clinical course of patients with read numbers.

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Product ANDA

Listed Drug

PRECAUTIONS

General: Soecial Risk Patients: As with any opioid analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Eiixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-1 hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

PREDAUTIONS

General: Spanie: Risk Evipanta, 14 is that in a transport agent, hydrocodone orientate and acetaminouner facilities should be used from baundo an algebra agent, hydrocodone orientate and acetaminouner facilities should be used from the acetaminouner facilities and indicate which severe in the facilities or the all facilities and the possibility of resonancy decreasion should be absented and the possibility of resonancy decreasion should be possible to the possibility of resonancy decreasion should be possible to the possibility of resonancy decreasion should be possible to the possibility of resonance to the possibility of the possibility

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Laboratory Tests: 'n patients livin' se ene nedat dior renai disease, effects of therapy should di maniforati with serial wer and or renai function tests.

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Brand Name Generic Name

ANDA Product

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be The withdrawal signs include physically dependent. rritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on tursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many trugs are excreted in human milk and because of the cotential for serious adverse reactions in nursing infants rom hydrocodone and acetaminophen, a decision should be hade whether to discontinue nursing or to discontinue the arug, taking into account the importance of the drug to the nother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, ethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood

Gastrointestinal System: Prolonged administration of nydrocodone bilartrate and acetaminophen elixir may Prolonged administration of produce constipation.

Listed Drug

Pregnancy:

Personance Effects Pregnant, Carest 1.2 Trace are no adequate and well-controlled studies pregnant fromen. Hydrododonal offeth assisted acastiminobiles idioasts should be used during pregnancy only it the ociential parent, just rise the potential risk to the fetus.

Pregnancy only it the ociential parent, just rise the potential risk to the fetus.

Pregnancy only it the ociential parent, rise set potential risk to the fetus operation of the fetus of the fetus of the ociential pregnancy and the fetus of the f Labor and Delivery: As with all nation of a solution before delivery may result in some logical of resonation of this product to the mother short before delivery may result in some logical of resonatory depression in the newborn, especially higher doses are used.

Mysising Motherst Acateminopher is express in breast milk in small amounts, but the significant of its effects on nursing infants is not known whether hydrocodone is expresed in human milk. Because many drugs are express in human milk and because of the potential to serious acresse reactions in nursing intensity from hydrocodone and acetaminophen, a decision should be made whether to discontinue hursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established

ADVERSE REACTIONS

The most frequently reported adverse reactions are injuried adverses, edition, nause and vomiting. These effects seem to be more prominent in amoulatory than in noncomposition patients, and some of these adverse reactions may be alleviated if the patient lies down.

Central Nervous System: Orowsiness, mental clouding, letnargy, impairment of mental and physical performance, anxiety, feat, dysonoma, osyonic decendence, modo changes.

Gastrointestinal System: Protonged administration of hydrocoone bitarrate and acetaminocrataciets may produce constitution.

= Brand Name Generic Name

ANDA Product

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Hydrocodone bitartrate may Respiratory Depression: produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Hydrocodone Bitartrate and Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Fsychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, aithough some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Serious overdose with hydrocodone is <u>Hydrocodone:</u> characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Listed Drug

Genitourinary System: Urereral spasm, spasm of vesical sphinoters and urinary retention habeen reported with opiates.

Respiratory Depression: Hydrocodone bitarrrate may produce dose-related respirator decression by acting directly on brain stem respiratory centers (see OVERDOSAGE). Dermatological: Skin rash, prontes.

The following adverse drug events may be corne in mind as potential effects of adetaminochia affergic reactions, rash, thromocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrococione Bitaritate and Acetantinophen Tablets are classified as Sunecula il controlled substance.

Scinecula II controlled substance:

Abuse and Dependence: Psychic decendence: physical decendence: and tolerance may develuence research administration of nationics: therefore, this product should be prescribed; administrated with daution. However, psychic decendence is unikely to develop when hydrodocobitationate and castaminiopher tablets are used for a short time for the treatment of pain.

Physical decendence, the condition in which continued administration of the drug is required brained that appearance of a withdraward syndrome, assumes definically significant procedule only after several, weeks, of continued narodoc use, auticupin some mid degree of only offer several, weeks, of continued narodoc use, auticupin some mid degree of only decendence may develop after a "law days of narodoc therapi. Tolerance, in which increase in large bosse are recurred in order to procluce the same degree of analyses is manifested initially a shortance duration of analgesic effect, and subsequently, by decreases in the intensit, analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE
Following an acuta prenosage, toxicity may result from hydrocozone or acataminochen

Signs and Symptoms

<u>Homographs</u> Serbus diversase with hydrocodome is characterized by resolvatory decression decreasion decreases in resolvatory rate and/or tips indicate. Chayne-Stores resolvation dyanosis, exits

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4

AND A Product

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dosedependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathanic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetarninophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

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sommolande progressing to studor or coma iskeletal muscia nacciony, coid and clammy skin lan sometimes, bradycardid and hypotension. In severa diverdosaça, aphaa, circulatory collads-cardidd arrest and death may octur.

Carotto Affect and death may occur Ansight normally in adelementarian defocação dose-decendent, ocientially fatal necatio necros is the most serious acterias effect. Renai turbular necross hypodytycemic como an thromodytocenia may also occur. Barry symptoms following a posentally necations orientose may include, hauses, romitio diaprofesis and general mais as Clinica and laboratory, suidence of necatio foxicity may not o acceleration of 12 hours post-registion. In social, necatio foxicity, has rarely deer reported with acute of lengoses or less than 10 gram or fatalities with less than 15 grams.

or farsitizes with less than 15 grams.

Trestment: A single or must be overcose with hydrocodoge and acetaminochien is a potential lethal polytropy precise. and constitution with a regional poson control center is recommence. Immediate treatment induces supported discretization of the control center is recommence. Immediate treatment induces supported discretization of the center of the unconscious center of the center of the unconscious center of the center of the center of the unconscious center of the center of the center of the unconscious center of the center of the unconscious center of the center of the center of the unconscious center of the center of the unconscious center of the center of the center of the unconscious center of the center of the center of the unconscious center of the center o

Injudent information accounts due to acestaminopnen overcoos, vistamin K should be administers intratectory. In a rocal antiagonist, can reverse respiratory decreasion and doma associated in operation and come associated with operation of the control expenses. Melevoral hydrocomorpis 0.4 mg to 2 mg is given parenterally. Since the duration of section of typercoordine may exceed that of the naioxone, the patient should be vect and continuous surveillance and received based of the antiagonist should be administered as need to maintain accounts of carefully significant resolvatory or cardiovascular decreasion.



If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is two tablespoonfuls (30 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a clear. fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 650 mg acetaminophen per 30 mL, with 7% alcohol. It is supplied as follows:

10mg/650 mg per 30 mL: 16 oz. Bottles 4 oz. Bottles 30 mL Unit Dose Cups

NDC 0121-0718-16 NDC 0121-0718-04 NDC 0121-0718-30

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC. Greenville, SC

Listed Drug

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2.5 mg/500 mg 5 ma 500 ma

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets. The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

7.5 mg/500 mg The usual adult dosage is one tablet every four to six hours as needed for pair. The total daily dosage should not exceed 6 tablets. The usual adult dosage is one tablet every four to six hours as needed for pair. The total daily dosage should not exceed 5 tablets. 7.5 mg/750 mg

pain. The total daily dosage should not exceed a tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets. 7:5 mg:550 mg 10 mg. 500 mg

The usual adult dosage should not exceed 6 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total adult dosage is one tablet every four to six hours as needed for pain. The usual adult dosage is one tablet every four to six hours as needed for pain. The total dosage should not exceed 6 tablets. 10 mg. 850 mg

HOW SUPPLIED
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7.5 ma. 500 ma

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Bottes of 100 _____/ICC \$2541-502-01

Bottes of 500 _____/ICC \$2541-502-05

Watson Laboratories

5 mg 300 mg

Revised December 15, 1997 13100-1

Brand Name/ Generic Name

02/00

changed due to dosage form

Controlled Room Temperature changed to current USP 24



Exhibit D



Product ANDA

Listed Drug

FRONT OF LABEL:

NDC 0121-0718-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg

650 mg

10.mg/650 mg per 30 mL

Hydrocodone bitartrate. USP (Warning: May be habit forming) Acetaminophen, USP Alcohol 7 % R, ONLY

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

"ISUAL DOSAGE: See package insert complete prescribing information. ot No. Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). Store at controlled room temperature / 20° - 25° C (68° - 77° F)



NDC 52544-503-01 HYDROCODONE BITARTRATE and **ACETAMINOPHEN** TABLETS, USP

CAUTION: Federal 'aw prohibits dispensing without prescription. 100 TABLETS

12592

= Brand Name | Generic Name

change due to dosage form

Controlled Room Temperature changed to current USP 24 Exhibit E



NDC 0121-0718-30

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

10 mg/650 mg per 30 mL

Alcohol 7%

Preservative: Methylparaben 0.15%

pH Range: 4.0 - 5.0

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

 $10 \times 30 \text{ mL}$

This unit-dose package is not child-resistant. Store at controlled room temperature, 20° - 25° C (68° - 77° F)

R, ONLY

FOR INSTITUTIONAL USE ONLY PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605



FRONT OF LABEL:

NDC 0121-0718-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/650 mg per 30 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming) Acetaminophen, USP Alcohol 7% R, ONLY

10 mg

650 mg

4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). Store at controlled room temperature 20° - 25° C (68° - 77° F)



FRONT OF LABEL:

NDC 0121-0718-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/650 mg per 30 mL

Hydrocodone bitartrate, USP
(Warning: May be habit forming)
Acetaminophen, USP
Alcohol 7%
R_x ONLY
16 fl oz (473 mL)

10 mg

650 mg

10 11 02 (113 122)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). Store at controlled room temperature 20° - 25° C (68° - 77° F)



Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0718-) has been packaged in the following container/closure systems:

- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
- Bottle: 16 oz. Brown HDPE BL-16 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 6. Bottle: 4 oz. Amber PET 24-400 container Cap: 24-400 White Clic-Loc with P/RVTLF Liner
- 7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin. Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.